

(19)



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European Patent Office
Office européen des brevets



(11)

EP 0 605 193 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
05.03.2003 Bulletin 2003/10

(51) Int Cl.7: **A61K 31/40, A61K 31/445,
A61K 31/55**

(21) Application number: **93310438.2**

(22) Date of filing: **22.12.1993**

(54) Use of benzothiophenes for treatment of hypercholesterolaemia

Verwendung von Benzothiophene zur Behandlung von Hypercholesterolämie

Utilisation des benzothiophènes pour le traitement de l'hypercholestérolémie

(84) Designated Contracting States:
**AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT
SE**

(30) Priority: **22.12.1992 US 995222**

(43) Date of publication of application:
06.07.1994 Bulletin 1994/27

(60) Divisional application:
02013421.9 / 1 238 667

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Description

[0001] The present invention relates to the discovery that the compound raloxifene and its pharmaceutically acceptable salt and solvates are useful for lowering serum cholesterol.

[0002] All mammalian cells require cholesterol as a structural component of their cell membranes and for non-sterol end products. The very property, however, that makes cholesterol useful in the cell membranes, its insolubility in water, also makes it potentially lethal. When cholesterol accumulates in the wrong place, for example within the wall of an artery, it cannot be readily mobilized and its presence leads to the development of an atherosclerotic plaque. Elevated concentrations of serum cholesterol associated with low density lipoproteins (LDL'S) have been demonstrated to be a major contributing factor in the development and progression of atherosclerosis.

[0003] Estrogen, particularly when taken orally, lowers plasma levels of LDL and raises those of the beneficial high density lipoproteins (HDL'S). Long-term estrogen therapy, however, has been implicated in a variety of disorders, including an increase in the risk of uterine cancer and possibly breast cancer, causing many women to avoid this treatment. Recently suggested therapeutic regimens, which seek to lessen the cancer risk, such as administering combinations of progestogen and estrogen, cause the patient to experience unacceptable bleeding. Furthermore, combining progesterone with estrogen seems to blunt the serum cholesterol lowering effects of estrogen. The significant undesirable effects associated with estrogen therapy support the need to develop alternative therapies for hypercholesterolemia that have the desirable effect on serum LDL but do not cause undesirable effects.

[0004] Attempts to fill this need by the use of compounds commonly known as antiestrogens, which interact with the estrogen receptor and/or bind what has been termed the antiestrogen binding site (AEBS), have had limited success, perhaps due to the fact that these compounds generally display a mixed agonist/antagonist effect and are subject to the same adverse effects associated with estrogen therapy.

[0005] The current invention provides methods for lowering serum LDL levels without the associated adverse effects of estrogen therapy, and thus provides an effective and acceptable treatment for hypercholesterolemia.

[0006] Certain 2-phenyl-3-arylbenzothiophene compounds were in a group of compounds first developed by C. David Jones and Tulio Suarez as anti-fertility agents (see U.S. Patent No. 4,133,814, issued January 9, 1979). Jones later found a group of these compounds to be useful for antiestrogen and antiandrogen therapy, especially in the treatment of mammary and prostatic tumors (see U.S. Patent 4,418,068, issued November 29, 1983). One of these compounds, the compound of the present invention was clinically tested for a brief time for the treatment of breast cancer. That compound is called raloxifene (formerly called keoxifene).

[0007] This invention provides the use of raloxifene, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament useful for lowering serum cholesterol levels.

[0008] The current invention concerns the discovery that raloxifene is useful for lowering serum cholesterol levels. Methods of treatment associated with this invention comprise administering the compound raloxifene or a pharmaceutically acceptable acid addition salt or solvate thereof, to a patient in need of lower serum cholesterol levels. The present method includes both medical therapeutic and/or prophylactic treatment, as appropriate. Generally, the compound is formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration, or administered by the intramuscular or intravenous routes. The compound can be administered transdermally, and is well suited to formulation as sustained release dosage forms and the like.

[0009] The compound raloxifene lowers serum cholesterol levels in animals and should be particularly useful for lowering cholesterol levels in humans. Excess serum cholesterol may result from a variety of conditions and disorders, including a lack of endogenous estrogen such as occurs in women following cessation of menstruation due to natural, surgical, or other processes, and patients having gonadal dysgenesis.

[0010] Raloxifene is a nonsteroidal compound that exhibits high affinity for conventional estrogen receptors in primary sex target tissues. However, it elicits minimal estrogenic responses in those tissues, and actually serves as a potent antagonist of natural estrogens such as estradiol. In contrast to other structurally distinct antiestrogen compounds, the compound raloxifene is able to antagonize classical estrogenic responses in primary sex target tissues while eliciting an estrogenic response on serum cholesterol levels. This dichotomy indicates selective agonist/antagonist actions on specific target cells which are highly desirable in treating hypercholesterolemia. Thus, the current invention allows a method of lowering serum cholesterol levels, comprising administering to a patient an amount of the compound raloxifene that lowers serum LDL levels, but does not significantly affect the primary sex target tissues. This combination of features allows for long-term treatment of the chronic ailment with little risk of developing the undesirable effects of customary estrogen replacement therapy.

[0011] The biological action of raloxifene is complex and may be unrelated to the detectable presence of the parent compound in the blood. Following oral administration of raloxifene (administered as the hydrochloride), to human subjects in the clinic, the parent compound was not detected in the serum of those subjects. It was determined that following oral administration, the compound was extensively conjugated to the glucuronidated form. Although no biological endpoints were measured in the human recipients, there was concern that the compound was not bioavailable.

[0012] Experiments were undertaken to address the bioavailability issue in laboratory animals where biological activity could be assessed. The animal studies indicated that raloxifene was maximally active in inhibiting both uterine uptake of tritiated-estradiol and the normal uterotrophic response to estradiol even under conditions where raloxifene was extensively conjugated in the plasma of the animals. Moreover, the conjugate, isolated from the urine of human subjects treated with raloxifene, displayed significant antiestrogenic/antiuterotrophic activity when administered intravenously to rats, and inhibited the interaction of tritiated-estradiol with rat uterine estrogen receptors in a manner similar to the parent compound at temperatures approaching physiologic conditions. Since these compounds did not bind at 4°C, these studies suggested the conjugated compound may have been converted to the parent form at the site of action, presumably by the action of β -glucuronidase. Such conversion may contribute to the activity of the compound. β -Glucuronidase is fairly ubiquitous and would presumably be available for converting the conjugated compound to the parental form if required for activity. Therefore, conjugation of raloxifene is not considered to be necessarily detrimental to its bioavailability.

[0013] Thus, the method of treatment facilitated by this invention is practiced by administering to a patient an amount of raloxifene, or a pharmaceutically acceptable salt or solvate thereof, that is effective to lower serum cholesterol levels. A particular benefit of this method is that it avoids potentially harmful and unacceptable estrogenic side effects. The present method includes both medical therapeutic and/or prophylactic treatment, as appropriate.

[0014] The method also includes the administration of raloxifene and estrogen, either independently or in combination. The term estrogen as used herein refers to any compound which approximates the spectrum of activities of the naturally acting molecule which is commonly believed to be 17 β -estradiol. Examples of such compounds include estriol, estrone, ethynyl estradiol, Premarin (a commercial preparation of conjugated estrogens isolated from natural sources - Ayerst), and the like. Again, due to the selective agonist/antagonist properties of raloxifene, this combination provides the benefits of estrogen therapy without the concomitant adverse effects associated with estrogen therapy alone.

[0015] Raloxifene and its pharmaceutically acceptable salts can be made according to established procedures, such as those detailed in U.S. Patent Nos. 4,133,814 and 4,418,068.

[0016] Raloxifene forms acid and base addition salts with a wide variety of organic and inorganic acids and bases and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl-substituted alkanic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Typical salts include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, β -hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propionate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like.

[0017] In addition, raloxifene may form solvates with water or organic solvents such as ethanol. These solvates are also contemplated for use in the methods of this invention.

[0018] Bases commonly used for formation of salts include ammonium hydroxide and alkali and alkaline earth metal hydroxides, carbonates and bicarbonates, as well as aliphatic and aromatic amines, aliphatic diamines and hydroxyalkylamines. Bases especially useful in the preparation of addition salts include ammonium hydroxide, potassium carbonate, sodium bicarbonate, calcium hydroxide, methylamine, diethylamine, ethylene diamine, cyclohexylamine and ethanolamine.

[0019] The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.

[0020] In another aspect, this invention provides a process for the preparation of a pharmaceutical composition which comprises admixing raloxifene, or a pharmaceutically acceptable salt or solvate thereof, prepared in known manner with suitable inert carriers and finishing the mixture to a pharmaceutical formulation suitable for use in lowering serum cholesterol levels.

[0021] This invention also contemplates a pharmaceutical formulation adapted for lowering cholesterol levels, comprising as an active ingredient the compound raloxifene, or a pharmaceutically acceptable salt or solvate thereof.

[0022] Pharmaceutical formulations can be prepared by procedures known in the art. For example, the compound, either alone or in combination with estrogen, can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and

silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinylpyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as agaragar, calcium carbonate, and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

[0023] The compound, either alone or in combination with estrogen, can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes. Additionally, the compound, either alone or in combination with estrogen, can be formulated as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

[0024] The particular dosage of raloxifene required to lower serum cholesterol levels according to this invention will depend upon the severity of the condition, the route of administration, and related factors. Generally, accepted and effective daily doses will be from about 0.1 to about 1000 mg, and more typically from about 50 to about 200 mg. Such dosages will be administered to a patient in need of treatment from once to about three times each day, or more often as needed to effectively lower serum cholesterol levels. Generally, accepted and effective daily doses of estrogen will be from about 0.01 to about 4.0 mg, and more typically from about 0.1 to about 2.0 mg. Such doses are administered to a patient in need of treatment from once to about three times a day, or more often as needed.

[0025] The method of lowering serum cholesterol levels is useful in men, as well as women. The substantial absence of estrogenic response should allow men to benefit from this invention without evidencing the feminizing response of estrogen or estrogen agonists such as gynecomastia. The method is especially useful in women, preferably estrogen-deficient women. The estrogen deficiency could occur naturally, such as post-menopausal, or surgically. Patients undergoing or having undergone long-term administration of corticosteroids and those having gonadal dysgenesis may also employ the method of the present invention.

[0026] It is usually preferred to administer raloxifene in the form of an acid addition salt, as is customary in the administration of pharmaceuticals bearing a basic group, such as the piperidino ring. It is also advantageous to administer such a compound by the oral route to an aging human (e.g. a post-menopausal female).

[0027] The following are examples of oral dosage forms useful in this invention.

Capsules

[0028] Hard gelatin capsules are prepared using one of Formulations 1-4:

Formulation 1:	
Ingredient	Quantity (mg/capsule)
Raloxifene hydrochloride	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 2:	
Ingredient	Quantity (mg/capsule)
Raloxifene hydrochloride	5
Starch, NF	108
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 3:	
Ingredient	Quantity (mg/capsule)
Raloxifene hydrochloride	10

(continued)

Formulation 3:	
Ingredient	Quantity (mg/capsule)
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 4:	
Ingredient	Quantity (mg/capsule)
Raloxifene hydrochloride	50
Starch, NF	150
Starch flowable powder	397
Silicone fluid 350 centistokes	3.0

Tablets

[0029] Tablets are prepared using Formulation 5:

[0030] Tablets each containing 0.1 - 1000 mg of Raloxifene hydrochloride are made up as follows:

Formulation 5:	
Ingredient	Quantity (mg/tablet)
Raloxifene hydrochloride	0.1 - 1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

[0031] Raloxifene hydrochloride, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

[0032] The following test examples illustrate the invention.

Test Procedure

[0033] In the examples illustrating the methods, a post-menopausal model was used in which effects of different treatments upon circulating lipids were determined.

[0034] Seventy-five day old female Sprague Dawley rats (weight range of 200 to 225 g) were obtained from Charles River Laboratories (Portage, MI). The animals were either bilaterally ovariectomized (OVX) or exposed to a Sham surgical procedure at Charles River Laboratories, and then shipped after one week. Upon arrival, they were housed in metal hanging cages in groups of 3 or 4 per cage and had *ad libitum* access to food (calcium content approximately 0.5%) and water for one week. Room temperature was maintained at 22.2° ± 1.7° C with a minimum relative humidity of 40%. The photoperiod in the room was 12 hours light and 12 hours dark.

Dosing Regimen/Tissue Collection.

[0035] After a one week acclimation period (therefore, two weeks post-OVX) daily dosing with test compound was

initiated. All compounds were administered orally at 1 ml/kg body weight unless otherwise stated. 17 β -Estradiol was administered subcutaneously in a 20% polyethylene glycol vehicle: 17 α -ethynyl estradiol and the test compound were given orally, unless otherwise stated, as a suspension in 1% carboxymethylcellulose or 20% cyclodextrin. Animals were dosed daily for 4 days. Following the dosing regimen animals were weighed and anesthetized with a ketamine: Xylazine (2:1, V:V) mixture, and a blood sample was collected by cardiac puncture. Each animal was then sacrificed by asphyxiation with CO₂; the uterus was removed through a midline incision and a wet weight was determined.

Cholesterol Analysis.

[0036] Blood samples were allowed to clot at room temperature for 2 hrs, and serum was obtained following centrifugation for 10 min at 3000 rpm. Serum cholesterol was determined using a Boehringer Mannheim Diagnostics high performance cholesterol assay. Briefly, the cholesterol was oxidized to cholest-4-en-3-one and hydrogen peroxide. The hydrogen peroxide was then reacted with phenol and 4-aminophenazone in the presence of peroxidase to produce a p-quinone imine dye, which was read spectrophotometrically at 500 nm. Cholesterol concentration was then calculated against a standard curve. The entire assay was automated using a Biomek Automated Workstation.

Uterine Eosinophil Peroxidase (EPO) Assay.

[0037] Uteri were kept at 4° C until time of enzymatic analysis. The uteri were then homogenized in 50 volumes of 50 mM Tris buffer (pH - 8.0) containing 0.005% Triton X-100. Upon addition of 0.01% hydrogen peroxide and 10 mM o-phenylenediamine (final concentrations) in Tris buffer, increase in absorbance was monitored for one minute at 450 nm. The presence of eosinophils in the uterus is an indication of estrogenic activity of a compound. The maximal velocity of a 15 second interval was determined over the initial, linear portion of the reaction curve.

Sources of Compounds:

[0038] 17 β -estradiol, 17 α -ethynyl estradiol and tamoxifen were obtained from Sigma Chemical Co., St. Louis, MO.

Experimental Groups:

[0039] All experimental groups were comprised of five or six animals.

INFLUENCE OF RALOXIFENE ON SERUM CHOLESTEROL

[0040] The results of control treatments are presented in Table 1. In summary, ovariectomy of the rats caused an increase in serum cholesterol as compared to intact vehicle treated controls. Estrogen, administered in the orally active form of ethynyl estradiol (EE₂), caused a decrease in serum cholesterol in a dose dependent manner, but it also exerted a stimulatory action on the uterus resulting in uterine weights approaching that of an intact rat when administered at 100 μ g/kg/day. Results are reported as the mean of measurements from 5 to 6 rats \pm the standard error of the mean.

[0041] In these studies, raloxifene, administered as the hydrochloride salt, also caused a serum cholesterol decrease in a dose dependent manner; however, only minimal increase of uterine weight over the ovariectomized controls was present in these animals. The effects of raloxifene are represented in Table 2. Accordingly, each point reflects the responses of 5 to 6 rats and depicts a typical dose response curve for raloxifene in this model. Results are reported as the mean \pm the standard error of the mean.

TABLE 1

	Serum Cholesterol (mg/dL)	Uterine Weight Ratio (mg uterus/g body weight)	EPO Activity (m OD/min)
Ovariectomy control (0.3 mL CMC)	81.3 \pm 13.4	0.48 \pm 0.04	5 \pm 2
Intact control (0.3 mL CMC)	72.6 \pm 14.6	1.70 \pm 0.12	216 \pm 32
EE ₂ 0.1 mg/kg	46.5 \pm 5.8	1.45 \pm 0.08	366 \pm 17

TABLE 2

	Serum Cholesterol (mg/dL)	Uterine Weight Ratio (mg uterus/g body weight)	EPO Activity (m OD/min)
Ovariectomy control (0.3 mL CMC)	87.5 ± 8.1	0.45 ± 0.02	4.8 ± 1.6
EE ₂ 0.1 mg/kg	8.1 ± 1.6	1.01 ± 0.03	295.1 ± 32.5
raloxifene 0.01 mg/kg	57.5 ± 6.9	0.54 ± 0.04	6.6 ± 1.4
raloxifene 0.10 mg/kg	35.3 ± 3.2	0.54 ± 0.04	5.8 ± 0.6
raloxifene 1.00 mg/kg	31.6 ± 3.4	0.56 ± 0.04	7.2 ± 2.0

[0042] Raloxifene was administered, as the hydrochloride salt, alone or in combination with 17 β -estradiol. Rats treated with raloxifene alone had uterine weights which were marginally higher than the ovariectomized controls and much less than those of 17 β -estradiol treated rats, which approached those of the intact controls. Conversely, raloxifene treatment substantially reduced serum cholesterol in ovariectomized rats. When given in combination with 17 β -estradiol, the 17 β -estradiol did not appreciably reduce the effects of raloxifene on serum cholesterol. The results are shown in Table 3.

TABLE 3

Experiment A	Serum Cholesterol (mg/dL)	Uterine Weight Ratio (mg uterus/g body weight)	EPO Activity (m OD/min)
Ovariectomy control (0.3 mL CMC)	47.8 ± 8.2	0.62 ± 0.04	8 ± 2
Intact control (0.3 mL CMC)	48.6 ± 7.3	2.25 ± 0.14	245 ± 27
17 β -estradiol 0.1 mg/kg	39.6 ± 4.6	1.41 ± 0.04	403 ± 55
17 β -estradiol 0.1 mg/kg + raloxifene 10 mg/kg	19.3 ± 4.3	0.99 ± 0.04	83 ± 31
raloxifene 10 mg/kg	25.6 ± 7.1	0.68 ± 0.04	2 ± 1

[0043] The ability of raloxifene to lower serum cholesterol was compared to that of tamoxifen (SIGMA, St. Louis, Mo). Tamoxifen, a well known antiestrogen currently used in the treatment of certain cancers, has been shown to lower serum cholesterol (see for example, Love, R., et al., *J. Nat. Can. Inst.*, **82**, 1327-1332 (1990)). A range of doses of raloxifene and tamoxifen was administered orally to ovariectomized rats as in the previous evaluation. Although both agents displayed the ability to lower serum cholesterol while evoking only modest uterotrophic activity, as identified by gains in uterine weight, a comparison of several histological parameters demonstrated a marked difference between the rats treated with these agents. The data are set forth in Tables 4 and 5, *infra*.

[0044] Increases in epithelial height are a sign of estrogenicity of therapeutic agents and may be associated with increased incidence of uterine cancer. When raloxifene was administered as described *supra*, there was no statistically measurable increase in epithelial height over the ovariectomized controls. This result was in contrast to the results seen with tamoxifen and estrogen. At all doses given, tamoxifen increased epithelial height equal to that of an intact rat. Estradiol treatment increased epithelial height to a thickness greater than intact rats.

[0045] Estrogenicity was also assessed by evaluating the adverse response of eosinophil infiltration into the uterus. Raloxifene did not cause any increase in the number of eosinophils observed in the stromal layer of ovariectomized rats while tamoxifen caused a substantial increase in the response. Estradiol, as expected, caused a large increase in eosinophil infiltration.

[0046] Little or no difference was detectable between raloxifene and tamoxifen effects on thickness of the stroma and myometrium. Both agents caused an increase in these measurements that was much less than the effect of estrogen.

[0047] A total score of estrogenicity, which was a compilation of all four parameters, showed that raloxifene was substantially less estrogenic than tamoxifen.

TABLE 4

	Serum Cholesterol mg/dL	Uterine Weight Ratio (mg uterus/g body weight)	EPO Activity (m OD/min)
Ovariectomy control (0.3 mL CMC)	61.4 ± 3.6	0.42 ± 0.05	4.3 ± 0.2
EE ₂ 100 µg/kg	9.1 ± 2.0	0.93 ± 0.08	155.6 ± 45.4
raloxifene 1 mg/kg	35.8 ± 4.1	0.54 ± 0.03	5.0 ± 0.6
tamoxifen 1 mg/kg	36.5 ± 2.8	0.76 ± 0.04	130.4 ± 31.4

TABLE 5

	Epithelial Height	Stromal Eosinophils	Myometrial Thickness	Stromal Expansion
Ovariectomy control (0.3 mL cMc)	1.24 1.24	1.00 1.00	4.42 4.42	10.83 10.83
Intact control (0.3 mL CMC)	2.71	4.17	8.67	20.67
EE ₂ 100 µg/kg	3.42	5.17	8.92	21.17
raloxifene 1 mg/kg (subcutaneously)	1.67	1.17	5.42	14.00
tamoxifen 1 mg/kg (subcutaneously)	2.58	2.83	5.50	14.17

Claims

1. The use of raloxifene, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for lowering serum cholesterol levels in a human.
2. The use of raloxifene hydrochloride in the preparation of a medicament for lowering serum cholesterol levels in a human.
3. The use as claimed in claim 1, in the preparation of a unit dosage form adapted for the administration of from 0.1 to 1000 mg of raloxifene per dosage unit.
4. The use as claimed in claim 2, in the preparation of a unit dosage form adapted for the administration of from 0.1 to 1000 mg of raloxifene hydrochloride per dosage unit.
5. The use as claimed in any one of the preceding claims, wherein said human is a post-menopausal female.
6. The use as claimed in any one of the preceding claims, wherein said use is prophylactic.
7. The use as claimed in any one of claims 1 or 3-6, in the preparation of a unit dosage form adapted for the administration of from 50 to 200 mg of raloxifene per dosage unit.
8. The use as claimed in any one of claims 2-6, in the preparation of a unit dosage form adapted for the administration of from 50 to 200 mg of raloxifene hydrochloride per dosage unit.
9. The use as claimed in any one of the preceding claims, wherein said human is a post-menopausal female and said use is prophylactic.
10. The use as claimed in any one of the preceding claims, wherein said medicament is adapted for oral administration.

Patentansprüche

1. Verwendung von Raloxifen oder eines pharmazeutisch annehmbaren Salzes oder Solvats hiervon zur Herstellung eines Arzneimittels zur Verringerung der Serumcholesterinspiegel bei einem Menschen.
2. Verwendung von Raloxifenhydrochlorid zur Herstellung eines Arzneimittels zur Verringerung der Serumcholesterinspiegel bei einem Menschen.
3. Verwendung nach Anspruch 1 zur Herstellung einer Einheitsdosierungsform, die zur Verabreichung von 0,1 bis 1000 mg Raloxifen pro Dosierungseinheit angepaßt ist.
4. Verwendung nach Anspruch 2 zur Herstellung einer Einheitsdosierungsform, die zur Verabreichung von 0,1 bis 1000 mg Raloxifenhydrochlorid pro Dosierungseinheit angepaßt ist.
5. Verwendung nach einem der vorangehenden Ansprüche, worin der Mensch eine postmenopausale Frau ist.
6. Verwendung nach einem der vorangehenden Ansprüche, worin die Verwendung prophylaktisch ist.
7. Verwendung nach einem der Ansprüche 1 oder 3-6 zur Herstellung einer Einheitsdosierungsform, die zur Verabreichung von 50 bis 200 mg Raloxifen pro Dosierungseinheit angepaßt ist.
8. Verwendung nach einem der Ansprüche 2-6 zur Herstellung einer Einheitsdosierungsform, die zur Verabreichung von 50 bis 200 mg Raloxifenhydrochlorid pro Dosierungseinheit angepaßt ist.
9. Verwendung nach einem der vorangehenden Ansprüche, worin der Mensch eine postmenopausale Frau ist und die Verwendung prophylaktisch ist.
10. Verwendung nach einem der vorangehenden Ansprüche, worin das Medikament zur oralen Verabreichung angepaßt ist.

Revendications

1. Utilisation du raloxifène, ou d'un sel ou solvate de celui-ci, acceptable sur le plan pharmaceutique, dans la préparation d'un médicament pour abaisser les taux sériques de cholestérol chez un humain.
2. Utilisation du chlorhydrate de raloxifène dans la préparation d'un médicament pour abaisser les taux sériques de cholestérol chez un humain.
3. Utilisation selon la revendication 1, dans la préparation d'une forme posologique unitaire adaptée à l'administration de 0,1 à 1000 mg de raloxifène par dose unitaire.
4. Utilisation selon la revendication 2, dans la préparation d'une forme posologique unitaire adaptée à l'administration de 0,1 à 1000 mg de chlorhydrate de raloxifène par dose unitaire.
5. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle ledit humain est une femme post-ménopausique.
6. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle ladite utilisation est prophylactique.
7. Utilisation selon l'une quelconque des revendications 1 ou 3 à 6, dans la préparation d'une forme posologique unitaire adaptée à l'administration de 50 à 200 mg de raloxifène par dose unitaire.
8. Utilisation selon l'une quelconque des revendications 2 à 6, dans la préparation d'une forme posologique unitaire adaptée à l'administration de 50 à 200 mg de chlorhydrate de raloxifène par dose unitaire.
9. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle ledit humain est une femme post-

ménopausique et ladite utilisation est prophylactique .

- 10.** Utilisation selon l'une quelconque des revendications précédentes, dans laquelle ledit médicament est adapté à l'administration orale.

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